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# *Thyroid Cancer Following Exposure to Radioactive Iodine*

***Jacob Robbins, M.D. and Arthur B. Schneider, M.D., Ph.D.***

*NIH, NIDDK, Genetics and Biochemistry Branch, Bethesda, MD 20892 and University of Illinois at Chicago, Section of Endocrinology and Metabolism, Chicago, IL 60612*

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Although external radiation is a well-known cause of human thyroid cancer, the risk from exposure of the thyroid gland to internal radiation is not well defined. This is of practical importance because of the extensive use of radioactive iodine in medical practice and the potential for release of iodine radionuclides into the environment. The purpose of this review is to summarize what is known from the analysis of medical and accidental exposures and to provide perspective for interpreting the personal and population risks that might exist.

## *Radioiodine Isotopes and their Properties*

The radioiodine most used clinically is $^{131}$I, its moderately energetic gamma emission is suitable for external measurement of the quantity and localization, and its highly energetic beta emission and 8-day half life are appropriate for radiotherapy. An alternative for diagnostic use is $^{123}$I, its 13-hours half life and absent beta emission result in much lower thyroid radiation (100 times lower, per microcurie administered, than $^{131}$I) while its moderately energetic gamma emission permits external measurement, albeit for a shorter period of time. For laboratory use, $^{125}$I is usually preferred because of its long half life (60 days). It has very low energy X-ray and no beta emission. $^{124}$I, a positron emitter, is coming into use for PET scanning. It also has an energetic gamma emission, and its half life is 4.2 days.

Accidents leading to environmental contamination produce volatile radioiodines that include $^{131}$I and several others with shorter half lives. The most important from the standpoint of thyroid radiation exposure are $^{132}$I (2.3 hours), $^{133}$I (21 hours), and $^{131}$I (8 d), the first being the daughter of a volatile tellurium isotope, $^{132}$Te (78 hours). Other radioiodines are less important because of very short half lives or low abundance

## *Studies after Therapeutic and Diagnostic use of Radioiodine*

In the approximately 50 years during which $^{131}$I has been used to study and treat thyroid diseases, despite several extensive retrospective studies, no convincing evidence has come forth to implicate it as a cause of thyroid cancer. There are, however, several reasons why a carcinogenic potential may have been missed. In the studies of treatment of hyperthyroidism, the radiation dose to which the thyroid cells were exposed, at least several thousand cGy (rads), was high enough either to destroy them acutely or to induce lethal mutations [1–5]. The latter is evident from the gradual appearance of hypothyroidism with time in many patients treated with $^{131}$I for diffuse toxic goiter [6]. This would tend to abrogate an oncogenic mutation that could occur or be expressed. A recent study from England [7] reports a significant increase in thyroid cancer incidence and mortality but the numbers were small (9 cases and 5 deaths in a cohort of 7,417). Furthermore, the overall cancer incidence and mortality was decreased, and it could not be excluded that the relationships were with the disease (i.e., thyrotoxicosis) rather than with its treatment with $^{131}$I. In addition, almost all of the treated patients were young adults or older, and it is known that this age group is much less likely to develop thyroid cancer after radiation exposure [8,9]. In a few studies of children given therapeutic $^{131}$I for hyperthyroidism, no malignant nodules were found after the treatment (reviewed in [10]) but the statistical power to demonstrate oncogenesis in these small groups of patients was limited.

In the case of the diagnostic use of $^{131}$I, the most extensive studies were carried out in Sweden, making use of the excellent cancer registry in that country [11]. The

Address correspondence to: Jacob Robbins, M.D., National Institutes of Health, NIDDK, Genetics and Biochemistry Branch, Bldg 10, Rm 6C 201A, 10 Center Drive MSC 1587, Bethesda, MD 20892-1587, E-mail: jacobr@bdg10.niddk.nih.gov

average radiation dose to the thyroid was about 100 cGy and there was a slight (non-significant) excess of thyroid cancer over that expected in that population, 67 cancers in 34,104 exposed people compared to 50 expected. A smaller study that included thyroid palpation reported a small dose-response relationship in nodule formation [12]. These findings were attributed to the fact that the patients who had diagnostic testing with radioiodine had suspected or actual thyroid diseases and, therefore, were not representative of the general population. Again, the studied populations included few children who would have been more likely to develop thyroid cancer after radiation.

## *Studies after Accidental Exposure to Radioiodine*

There have been several attempts to evaluate the incidence of thyroid cancer in populations accidentally exposed to radioactive fallout. In this discussion, we start with the recent accident at Chernobyl, since that has provided the most powerful evidence confirming a relationship. It is also important at the outset to correct the frequent misinterpretation concerning the populations exposed to the atomic bomb explosions at Hiroshima and Nagasaki. Although the study of these Japanese populations provide some of the best and most detailed information about radiation-induced thyroid cancer in humans [8,9], the radiation was external and not internal because the volatile radionuclides were dispersed into the upper atmosphere, and did not contribute to local fallout.

### *Nuclear power station accidents*

The Chernobyl accident released about 40 MCi $^{131}$I into the environment [13]. In comparison, the accident at Three Mile Island released about 20 Ci of $^{131}$I, two million times less, and resulted in a population exposure far below that expected to produce thyroid cancer [14]. At Chernobyl, the initial radioactive cloud contained 68 MCi of $^{133}$I and 27 MCi of $^{132}$Te, and the release continued erratically for about 10 days. The resulting radioactive fallout was most intense in the northern regions of Ukraine and, especially, in southern Belarus, both countries at that time part of the USSR [15]. Extensive measurements have been made of the ground contamination by $^{137}$Cs and of its body content in residents of the contaminated area, and the ground contamination by $^{131}$I has been estimated, but this will need to be reevaluated because the distribution in soil samples of $^{137}$Cs and $^{129}$I, an extremely long-lived radioiodine in the fallout, may not be identical [16]. Many individuals in the heavily contaminated regions also had measurements of thyroid radioiodine content in the early days after the accident [17,18].

The thyroid radiation doses resulting from the accident are undergoing extensive reevaluation. The current estimates must be regarded as preliminary and, therefore, it is not yet clear whether the risk from radioiodine differs from that of external radiation [19]. The increase in thyroid cancer in the region's children indicates that the radiation exposure must have been in the range that can induce thyroid cancer [20] and a case-control study in Belarus has shown a strong relationship between thyroid cancer and the estimated thyroid dose particularly in cases from rural areas [21]. In that study, estimated doses ranged from D-6 cGy to 600 cGy. Although more than half of the cases had estimated doses under 30 cGy, the largest differences between cases and controls were in the range above 30 cGy. The best current estimate is that at least 90% of this radiation dose was derived from $^{131}$I [17,22], most of it coming from contaminated vegetable and dairy products, which is consistent with the observation that children in rural areas had the highest doses and the strongest relationship. The short-lived radioiodines would have entered the body mainly by inhalation and be more important in close-in areas.

Other contributing factors must also be taken into account. Potassium iodide in doses high enough to block radioiodine accumulation in the thyroid was administered, but was not begun until several days after the accident and its use was very erratic. The mild iodine deficiency in the region surrounding Chernobyl could also have affected the radiation dose by increasing the amount of iodine accumulated and increasing the size of the gland in which it was deposited, and it might also alter the radiation effect itself [23]. Despite these uncertainties, there is now an opportunity to derive a risk coefficient for radioiodine-induced thyroid cancer, as was previously achieved for external radiation [8,9]. Ongoing dose reconstruction [17] and prospective screening of a cohort of individuals exposed in childhood [24] may attain this goal.

When the first cases of thyroid cancer were reported, beginning in 1990, only 4 years after the accident, there was concern that they might have been an artifact of increased ascertainment [20], but it soon became obvious that this was not the case. The number of affected children increased rapidly and reached an unprecedented incidence for childhood thyroid cancer (Fig. 1) [20,25–29]. Before the end of the first decade, this increased in children under age 15yr on 26 April 1986, from a baseline of $< 1$ case per million per year, to $> 30/10^6$/yr in Belarus and $> 3/10^6$/yr in Ukraine. In the Gomel oblast of Belarus, a region with one of the highest levels

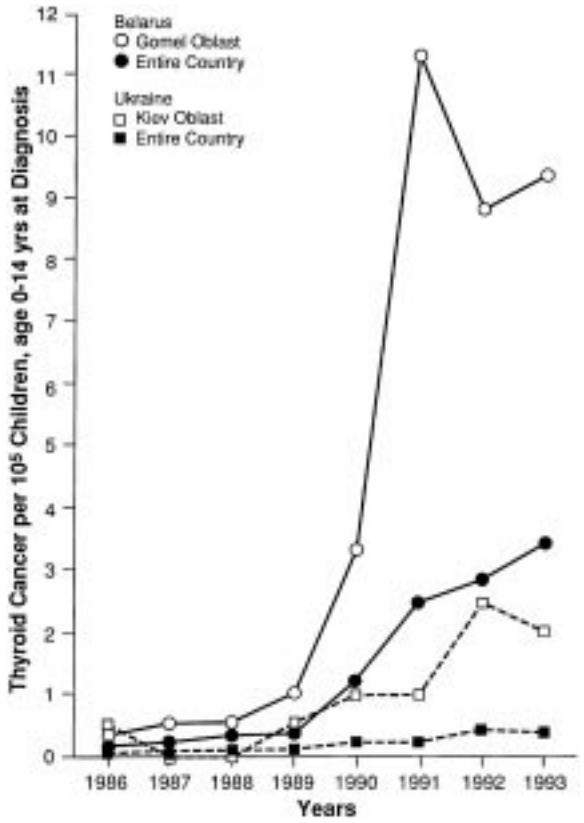


***Fig. 1.*** *Annual incidence of thyroid cancer per 100,000 children in Belarus and Ukraine and in the region of each republic with the highest contamination from the Chernobyl accident that began on April 26, 1986. Radioiodine release ended 10 days later. Reproduced with permission [20].*

of contamination, the incidence exceeded $100/10^6$/yr. Even more impressive is the fact that the incidence in children born after November 1986 has returned to what appears to be the pre-accident level [30].

Because radiation was the presumed cause of virtually all of the cases, the Chernobyl accident has afforded a unique opportunity to characterize the clinical behavior, pathological anatomy and molecular genetics of radiation-induced thyroid cancer. Essentially all of them were confirmed to be papillary carcinoma. In children, papillary thyroid carcinoma tends to be more aggressive than in young adults. Although its mortality is similarly low, it is more likely to grow rapidly, to invade the thyroid capsule and to metastasize to regional lymph nodes [31]. The post-Chernobyl cancers appeared to grow even more aggressively and to have an unusually high incidence of a newly described variant of papillary carcinoma termed ''solid/follicular'' [30,32,33]. As the term implies, it is a follicular variant of papillary carcinoma that contains an unusually high proportion of solid cellular architecture. The Chernobyl cancers also have a higher incidence of the translocated ret gene that forms the ret/PTC oncogene. This oncogene is characteristic of papillary thyroid cancer, and there are several variations depending on the gene with which ret combines (reviewed in [33]). The Chernobyl cancers have a higher proportion of the ret/PTC-3 variant [29,33,34]. Some of these differences are attributable to the younger age range of the post-Chernobyl cases, but a radiation etiology appears to be an important additional contributor.

Still unanswered are the questions whether radiation from the Chernobyl accident increased the incidence of thyroid cancer in those who were adults at the time of the accident, whether it increased the incidence of benign thyroid nodules, and the total number of thyroid cancers that will occur. Based on experience with external radiation the development of thyroid cancer in exposed children is expected to continue well into their adult life [9,35]. Eventually the number of cases will likely reach at least several thousand in excess of those normally occurring in older individuals.

### *Radioiodine fallout from nuclear weapons production and testing*

Because of the Chernobyl experience there has been increased interest in the possible consequences of the environmental contamination that resulted from the manufacture and testing of nuclear weapons. Three instances have received the most attention: the accidental exposure of Marshall Islanders to fallout from a nuclear bomb test on Bikini in 1954, the exposure of ''downwinders'' to I-131 releases from the Hanford facility in eastern Washington State, and contamination of the continental United States by fallout from atomic bomb detonations at the Nevada Test Site, during the 1940s and 1950s.

Before the Chernobyl accident, the Marshall Islands event provided the most convincing evidence that radioiodine could be the cause of thyroid cancer in humans. Between the 9th and 34th years after the exposure, 42 benign thyroid nodules and 9 papillary carcinomas were found among the 253 exposed residents on the islands of Rongelap, Sifo and Uterik. All but one of the cancers developed during adult life, but 6 of the 9 patients with cancer were under age 18 at the time of the accident. On Rongelap, the most heavily exposed island, 20 of the 24 children who were under age 10 or in utero at that time developed either a thyroid nodule or hypothyroidism [36,37]. The number of benign and malignant nodules exceeded the expected incidence in this small population, but the complexity of the exposure has made it impossible to derive an accurate risk estimate for radiation due to $^{131}$I. It has been estimated that 80 to 85%

of the internal radiation dose on Rongelap was actually from short-lived radioiodines [38]. The average internal dose in different age groups ranged from 250–5000 cGy and a number of the residents developed elevated serum TSH or overt hypothyroidism. In addition, the thyroid dose from external radiation was 190 cGy and this dose alone is in the carcinogenic range for young children. On Uterik, however, the internal dose averaged 48–670 cGy and only 11 cGy was externally derived. Despite these problems, it remains likely that radioiodine, if not $^{131}$I per se, was indeed the major cause of the thyroid nodules and cancers arising from the Marshall Islands accident.

Between 1944 and 1955, 0.74 MCl of $^{131}$I were released into the atmosphere from the Hanford Site, a facility engaged in nuclear weapons and fuel production, reprocessing and storage [39]. About 90% of the release occurred during 1945 and 1946. Because of the process employed, shorter-lived radioiodines were largely not involved. The most heavily exposed population resided to the east of the site and the median cumulative thyroid radiation dose to an infant or young child in the most contaminated region was estimated at 230 cGy (range 60–840 cGy) [40]. Between 1992 and 1997, a cohort of approximately 3,500 people who were young children (born 1940–1946) during the exposure period were screened for thyroid nodules by thyroid palpation and ultrasonography. Their individual thyroid radiation doses have been calculated on the basis of place of residence and dietary history, especially the source and quantity of milk intake. The analysis of these data has failed to show a significant correlation between the radiation dose and the occurrence of either benign or malignant thyroid nodular disease [41].

The continuing development of nuclear weapons led, during the 1950s, to a large number of test detonations at a site in southern Nevada [42]. These explosions were above ground and the resulting radionuclides were injected into the atmosphere and carried by prevailing winds predominantly in a northeasterly direction. As influenced by meteorological conditions, $^{131}$I was deposited in a spotty fashion over a large portion of the continental United States. The greatest ground deposition was in eastern Nevada, most of Utah, and adjacent areas in a few neighboring states. Reconstructed thyroid radiation doses, however, largely based on $^{131}$I concentration in milk, were high in much of the midwestern United States. In Washington County, Utah, where fallout was among the highest, the cumulative thyroid doses for milk-drinking children was $17 \pm 27$ cGy (mean $\pm$ SD) [43,44]. Average lifetime doses in Los Angeles, New York City and Salt Lake City were 0.3, 5 and 10 cGy, respectively [42].

An indicator of the possible health effects from the Nevada Test Site fallout is provided by the screening of a cohort of 4,831 children in Arizona, Nevada and Utah in whom thyroid radiation doses ranged from 0 to 460 cGy [43,45]. The 20-year follow up disclosed 8 papillary thyroid carcinomas, 11 benign thyroid neoplasms and 34 non-neoplastic thyroid nodules [43]. There was a statistically significant relationship between thyroid radiation dose and malignant plus benign neoplasms combined, but a significant correlation was not found for malignant or benign nodules analyzed separately. The borderline significance of this finding has been discussed [46].

In addition to the above, studies are currently under way in the former Soviet Union where there were large releases of radionuclides from nuclear weapons production and testing [47,48].

## *Methods for Protection Against Accidental Exposure*

In the event of an accidental release of radionuclides, protective measures that are needed depend on a number of factors, including the perceived danger, the identity of the radionuclides and whether they are volatile. General methods include isolation from the contamination (for example, remaining indoors or behind a barrier), evacuation of the contaminated area, and avoidance of ingestion or inhalation of contaminated food or air. In the case of radioiodine, there are two special considerations which afford important additional protection. One concerns the fact that iodine is concentrated in the milk of grazing animals such as cows and goats. Because the half lives of the radioiodines are short, 8-days for $^{131}$I, storage of dairy products before they are consumed is effective. The other is the fact that a number of methods are available to block the accumulation of iodine by the thyroid gland, because of its simplicity and its demonstrated effectiveness and safety, potassium iodide (KI) is the preferred agent [49,50].

A single oral dose of 130 mg KI (iodine = 100 mg) in an adult provides nearly complete blockade of radioiodine uptake for a few hours after administration, and $>$ 80% blockade for 24 hours. It can be given in liquid or tablet form, and tablets protected from light and moisture have a very long shelf life. For children, recommended doses of KI are 16 mg for a newborn, 32 mg for an infant, and 65 mg for ages 3 to 12 years [50]. Since the blockade falls to about 50% if KI is given several hours after exposure to radioiodine, it must be administered quickly, and preferably in anticipation of exposure. For this reason, adequate supplies of KI should be ready for immediate distribution when needed.

Because no more than a few doses of KI should be needed before other means of avoiding radioiodine

intake become available, it has a wide margin of safety as demonstrated by its extensive use in Poland after the Chernobyl accident [51]. Its safety extends to infants and pregnant women. Older people who may have autoimmune thyroid disease or nodular goiter are at risk for the development of hypo- or hyperthyroidism. Since children are much more susceptible to radiation-induced thyroid cancer, this age group should be the primary focus for KI distribution. For the same reason, the anticipated thyroid radiation dose requiring blockade might vary with age. Doses that have been suggested are 1 cGy for neonates, infants, children, adolescents and pregnant and lactating women, 10 cGy for adults under 40, and 5 Gy after age 40, the latter to prevent thyroid cell killing rather than oncogenesis [50]. The 1 cGy exposure dose is understood to be conservative but was recommended because of the demonstrated very low risk from KI administration in this population. For children and adolescents, however, an exposure limit of 5-10 cGy may be more reasonable. The Chernobyl studies should eventually provide a better basis for these recommendations.

## *Medical Surveillance and Care of Exposed Persons*

The same thyroid radiation doses used to recommend KI administration might also be used to govern advice in selecting exposed persons who require investigation for thyroid cancer. Complicating features, however, are the high incidence of thyroid nodular disease, including medically unimportant occult carcinoma, in the unexposed population and the extreme sensitivity of thyroid nodule detection by ultrasonography [52,53]. This is balanced by the fact that the background of thyroid nodular disease increases with age. Thus, young children have a low incidence of thyroid nodules, especially malignant ones ($< 1$ cancer per million), so that screening of exposed children as was done in the Chernobyl and Nevada Test Site regions is sensible, and the use of ultrasonography can be defended. In adults, whether they were exposed during adult life or as children, great care is needed to avoid overdiagnosis and unnecessary treatment. For example, in a group of patients exposed to external neck radiation, as many as 87% had detectable non-palpable nodules [54].

For these reasons, an Institute of Medicine committee has advised against screening the adult population of the USA who were exposed as children to the Nevada nuclear weapons tests [55]. To avoid overtreatment of occult nodules, the committee also recommended thyroid gland palpation as the key examination for thyroid cancer Suppression of TSH by thyroid hormone as a means of preventing cancer development also is not indicated [56]. When the radiation exposure dose is high, whether in children or adults, examination for hypothyroidism may be more important than screening for thyroid cancer [57].

## *Summary*

The thyroid gland is one of the most sensitive organs for radiation-induced oncogenesis and the magnitude of the risk from external radiation is well understood. This is not the case for internal radiation derived from the radioiodines, a matter of practical importance because of medical use and potential accidental exposure. This article reviews current knowledge derived from the follow-up of patients receiving diagnostic or therapeutic $^{131}$I and populations exposed to radioactive fallout. The latter includes the nuclear power station accident at Chernobyl and the results of atomic bomb development and testing at Hanford, the Nevada Test Site and the Marshall Islands. The most cogent information comes from Chernobyl where an epidemic of childhood thyroid cancer has followed exposure to radioiodine that was mainly $^{131}$I. Although much has been learned from this experience about the nature of radioiodine induced thyroid cancer in young children, the reconstruction of thyroid radiation doses is too preliminary to provide accurate knowledge of the risk in comparison to that from external radiation. In the Marshall Islands, much of the exposure was from short-lived radioiodines as well as external radiation, obviating the possibility to determine the risk from $^{131}$I. Exposure to $^{131}$I in the continental United States from atomic bomb testing is expected to have caused some thyroid cancers, but only in the immediate vicinity of the Nevada Test Site has any evidence of radiation-induced thyroid neoplasms been adduced. This evidence is minimally significant statistically, and not significant for thyroid cancer per se. Medical use of radioiodine has not been observed to cause thyroid cancer but very few of the patients studied were young children, the group most sensitive to thyroid radiation. Despite these limitations, this information is sufficient to make some suggestions concerning protective measures in the case of nuclear accidents and the follow up of individuals who have been exposed.

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